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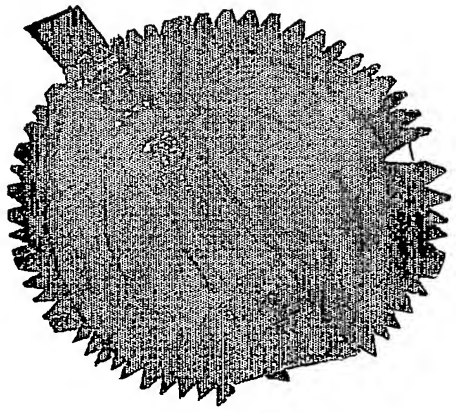
I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Provisional Specification*** *filed in connection with Application for Patent No.* ***27/Del/2004*** *dated* ***06th January 2004.***

Witness my hand this 13th day of May 2005.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1 0027DEC04

THE PATENT ACT, 1970 :- 6 JAN 2004
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT

BY THE ASSIGNEE AND LEGAL REPRESENTATIVE OF THE TRUE AND FIRST INVENTORS.

(See Section 7 , 5 (2), 54 and 135 , rule39)

We, **PANACEA BIOTEC LIMITED** of B-1 ,Extn. A/27 Mohan Co-operative, Indl. Estate, Mathura Road, New Delhi – 110044, A Company registered under " The Companies Act 1956.

Hereby declare :-

(i) That we are in possession of an invention for **"CONTROLLED RELEASE ANTIBIOTIC COMPOSITIONS"**.

(ii) That the provisional specification relating to this invention is filed with this application

(iii) That there is no lawful ground of objection to the grant of a patent to us.

(iv) Further declare that the inventors for the said invention are

RAJESH JAIN
Joint Managing Director
Panacea Biotec Limited.,
B-1 ,Extn. A/27
Mohan Co-operative,
Indl. Estate, Mathura Road,
New Delhi – 110044
INDIAN.

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SUKHJEET SINGH
General Manager – R & D
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B-1 ,Extn. A/27
Mohan Co-operative,
Indl. Estate, Mathura Road,
New Delhi – 110044
INDIAN.

(v) That we are assignee of the true and first inventors.

(vi) That our address for service in India is as follows :

Nagpaul & Associates
Patent & Trade Mark Attorneys
5/10, West Patel Nagar
New Delhi – 110008.

(vi) Following declaration was given by the inventors :

We, the true and first inventors for this invention declare that the applicants herein are our assignee

RAJESH JAIN	DR. KOUR CHAND JINDAL	SUKHJEET SINGH
Joint Managing Director	**Executive Vice President – R & D**	**General Manager – R & D**
Panacea Biotec Limited.,	Panacea Biotec Limited.,	Panacea Biotec Limited.,
B-1 ,Extn. A/27	B-1 ,Extn. A/27	B-1 ,Extn. A/27
Mohan Co-operative,	Mohan Co-operative,	Mohan Co-operative,
Indl. Estate, Mathura Road,	Indl. Estate, Mathura Road,	Indl. Estate, Mathura Road,
New Delhi – 110044	New Delhi – 110044	New Delhi – 110044
INDIAN.	INDIAN.	INDIAN.

(vii) That the best of my knowledge, information and belief, the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patents.

(viii) Following are the attachments with the application.

a. Complete Specification (3 copies)

b. Power of Authority.

c. Fee Rs. 3000/- by cash ~~cheque~~ ~~bearing No.~~ ~~dated~~ ~~Drawn on~~

We request that a patent may be granted to us for the said invention.

Dated this 6th day of January 2004

For Panacea Biotec Limited.,

Rajesh Jain
Joint Managing Director

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE
NEW DELHI

0027DEL04

16 JAN 2004

FORM 2

THE PATENTS ACT, 1970

(39 OF 1970)

Provisional Specification

(see Section 10; Rule 13)

CONTROLLED RELEASE ANTIBIOTIC COMPOSITIONS

Panacea Biotec Ltd.
B-1 Extn. A-27, Mohan Co-operative Industrial Estate,
Mathura Road,
New Delhi - 110 044

The following specification describes the nature of this invention:

CONTROLLED RELEASE ANTIBIOTIC COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to controlled release compositions of antibiotic, specifically, Amoxycillin sodium either alone or in combination with other antibiotic(s). The controlled release compositions are of non-disintegrating, non-eroding, non-bioadhesive and non-swelling type, intended to retain its geometrical shape throughout its transit in the gastro-intestinal tract. The controlled release composition is useful in providing therapeutically effective levels of the said antibiotic for extended periods of time. Moreover the said composition is not expected to compromise the bioavailability of the antibiotic under fed or fasted conditions.

BACKGROUND OF THE INVENTION

Amoxycillin is a beta-lactam widely used as a broad-spectrum antibiotic for treatment of a variety of common bacterial infections. Amoxycillin has known susceptibility to inhibition by beta-lactamases produced by resistant organisms. Amoxycillin is available in a variety of formulations, for instance as capsules, tablets, dry powders for reconstitution, chewable tablets, dispersible tablets etc. Amoxycillin is available as tablets of different strengths such as 250 mg, 500 mg, 875 mg, etc. The standard adult dose is 250 mg to 500 mg three times a day (tid). In addition, the 875 mg tablet is intended for dosing twice daily (bid) instead of 500 mg tid. A high dose of 3 g, bid is recommended for treatment of recurrent purulent infection of respiratory tract. Use of 1 g Amoxycillin is recommended as one arm of combination therapy, for eradication of helicobacter pylori in peptic ulcer disease.

In the past, attempts have been made to develop modified release/controlled release formulations of Amoxycillin. Such modified/controlled release tablets may provide better patient compliance since they need to be administered twice daily as compared to the 500 mg dose given tid.

European patent number EP1044680 discloses bilayered tablets comprising of an immediate release dose of a part of Amoxycillin and potassium clavulanate and a controlled release dose of a second part of Amoxycillin. The controlled release layer is a hydrophilic matrix. The above said composition suffers from the drawback that it

requires excess quantities of excipients for preparing bilayered tablets. This combined with the high dose of Amoxycillin results in a product which is too bulky and difficult to administer.

US Patent no. 5,690,959 discloses a composition prepared using hydrophobic material manufactured by a process of thermal infusion. Amoxycillin, being temperature sensitive, may undergo degradation if subjected to high temperatures for longer periods of time.

US Patent no. 6,399,086 discloses a pharmaceutical composition of Amoxycillin wherein 50% of the drug is released within 3-4 hours. The said composition is based on hydrophilic erodible polymers.

US Patent no. 6,368,635 discloses a solid matrix composition which is solid at ambient temperature, which comprises a viscogenic agent, such as an acrylic acid polymer, capable of developing viscosity on contact with water, as dispersed at least in the neighborhood of the surface layer of a matrix particle containing a polyglycerol fatty acid ester or a lipid and an active ingredient. The matrix may be such that a matrix particle containing a polyglycerol fatty acid ester or a lipid and an active ingredient has been coated with a coating composition containing at least one viscogenic agent. Such composition can adhere to the digestive tract and remain there for a prolonged period of time, thereby increasing the bioavailability of the active ingredient. Such gastric mucosa-adherent particles have unpredictable residence time in the stomach and are higly influenced by the gastric contents. Bioavailability of active agents from such compositions are highly variable.

European patent no. EP0526862 discloses a pharmaceutical composition of Amoxycillin with prolonged residence due to high density of the composition. The said composition suffers from the drawback that non-uniform release of active ingredient results due to variable passage of tablet into intestine by virtue of density itself resulting in significant bioavailability loss.

Hilton and Deasy, [J. Pharm. Sci. 82(7):737-743 (1993)] describe a controlled-release tablet of Amoxycillin trihydrate based on the enteric polymer hydroxypropylmethyl cellulose acetate succinate. This polymer suppressed the release of the drug in the presence of gastric pH but could enhance its release in the small intestine. Therefore, such a formulation cannot give the desired burst effect outlined in the present invention.

Single dose studies with a panel of fasting subjects showed that the tablets had a relative bioavailability of only 64.4%, probably because of the poorer absorption of Amoxycillin from the distal jejunum and ileum than from the duodenum and proximal jejunum. Other pharmacokinetic parameters confirmed a lack of therapeutic advantage of these factors over an equivalent dose of conventional capsule.

Hilton and Deasy [Int. J. Pharm. 86(1):79-88 (1992)] also describe a floating tablet of Amoxycillin trihydrate. A bilayer tablet was initially formed in which the controlled-release drug layer consisted of Amoxycillin and hydroxypropyl cellulose. This layer was bonded to a gas generating layer. However, when the two layers were joined together, the composite tablet failed to float and prematurely split along the joining of the two layers. Consequently, it was decided to abandon this approach in favor of a single-layer floating tablet. This tablet remained buoyant for 6 hours and had satisfactory in vitro sustained release. However, compared with conventional capsules in fasting humans at 500 mg equivalent dose of Amoxycillin, the relative bioavailability of the tablets were 80.5% and other pharmacokinetic parameters T(0.1 mug/ml) and T(0.5mug/ml) corresponding to the length of time for which the serum levels remained greater than or equal to 0.1 mug/ml and 0.5 mug/ml, respectively, indicated lack of improved efficacy.

Uchida et al. [Chem. Pharm. Bull. 37(12):3416-3419 (1989)] describe a preparation of Amoxycillin, microencapsulated in ethyl cellulose. These micro-capsules exhibited a sustained-release effect when administered to dogs. However, such effect could be foreseen, since the gastric pH of the dogs which were tested, is considerably higher than human gastric pH (pH of about 6 in beagle dogs, compared to pH of about 2 in humans). The Amoxycillin is much less soluble at pH 6 than at pH 2. One would expect to obtain a very quick release of the drug from the same microcapsules if administered to humans. Hence, such combination would not provide a controlled release of Amoxycillin

Arancibia et al. [Int. J. Clin. Pharmacol. Ther. Toxicol. 25(2):97-100 (1987)] investigated the pharmacokinetics and bioavailability of Amoxycillin trihydrate. They refer to controlled-release tablets, the composition of which is not described. In any case, no drug was detectable after 8 hours from oral administration and therefore this formulation had no advantage over conventional formulations.

Some of the compositions discussed in the art are prepared using hydrophilic swellable polymers. These compositions require the use of excessive quantities of release controlling agents. This, combined with high dose of Amoxycillin, results in a product which is too bulky to administer orally. In addition, these products have significant food effects resulting in variable bioavailability. Another approach available in the art involves the use of bioadhesive polymers. Such products are highly variable since bioadhesiveness is a property which is significantly dependent on the gastric contents. Presence of food in the stomach reduces the bioadhesive property resulting in reduced bioavailability. A third approach discussed in the art uses enteric polymers. Since Amocyxillin is predominently absorbed from proximal part of small intestine, enteric release of the drug results in loss of bioavailability. Hence there still exists a need for developing controlled release compositions of Amoxycillin, either alone or in combination with other antibiotic(s), devoid of limitations discussed above.

OBJECTIVE OF THE INVENTION

The present invention relates to controlled release compositions of antibiotic, either alone or in combination with other antibiotic(s).

Specifically, the present invention describes controlled release compositions of Amoxycillin sodium.

More specifically, the present invention relates to non-disintegrating, non-eroding, non-bioadhesive and non-swelling controlled release compositions of Amoxycillin sodium

SUMMARY OF THE INVENTION

The invention relates to the controlled release formulations of antibiotic either alone or in combination with other antibiotic(s) for maintaining concentrations above effective levels, for extended periods of time. Preferably, the invention relates to controlled release formulation of Amoxycillin sodium. The release mechanism involves predominantly diffusion and the product is in the form of a non-disintegrating tablet. The tablet maintains its geometric shape even after the drug has diffused from the system.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to controlled release formulation of antibiotic, either alone or in combination with other antibiotic(s), which is a non-mucoadhesive, non-disintegrating, non-swelling and non-eroding product. In an embodiment, the invention describes controlled release non-mucoadhesive, non-disintegrating, non-swelling & non-eroding type formulation of Amoxycillin sodium. The said composition retains its geometric shape throughout its stay in the gastro-intestinal tract. The product also has the advantage of showing minimal food effect. The drug release from the product is predominantly by diffusion mechanism.

In another embodiment, the present invention relates to the controlled release formulations of Amoxycillin sodium for maintaining concentrations above effective levels, for extended periods of time. The release mechanism involves predominantly diffusion and the product is in the form of a non-disintegrating tablet. The tablet maintains its geometric shape even after the drug has diffused from the system. In addition the formulation has been found to have a unique release profile with a monolithic structure. It gives a an initial burst release of approximately 20% - 40% within one hour for achieving blood levels equivalent to minimum inhibitory concentration, while maintaining these levels for an extended period of time. In another embodiment of the present invention, the controlled release tablets prepared using the said composition may provide better patient compliance since they need to be administered twice daily as compared to the 500 mg dose given tid.

The controlled release formulations prepared according to the said invention does not loose its geometric shape throughout its transit in the gastro-intestinal tract. Such a formulation does not involve the use of swellable polymers, hydrophobic waxy materials or mucoadhesive agents. Such a product may be prepared using polymers like polyvinyl pyrrolidone, polyvinyl acetate, methacrylic acid polymers; and the like either alone or in combination thereof. The controlled release composition of the present invention may be formulated as oral dosage forms such as tablets, capsules and the like. The examples given below serve to illustrate embodiments of the present invention. However they do not intend to limit the scope of present invention.

EXAMPLES

Example 1

	Ingredient		mg/tablet
i)	Amoxycillin sodium (equivalent to 750 mg Amoxycillin)	-	797
ii)	Lactose	-	100
iii)	Polyvinylpyrrolidone/Polyvinylacetate (PVP/PVA) co-polymer	-	200
iv)	Polyvinylpyrrolidone (PVP)	-	50
v)	Magnesium stearate	-	10
vi)	Talc	-	10

Sift ingredients (i) to (vi). Separately blend (i), (ii), (iii) and (iv). Slug and de-slug the blend. Mix with ingredients (v) and (vi), previously sifted & kept separately. Compress into tablets.

Example 2

	Ingredient		mg/tablet
i)	Amoxycillin sodium (equivalent to 750 mg Amoxycillin)	-	797
ii)	Lactose	-	150
iii)	Eudragit RS	-	75
iv)	Eudragit RL	-	150
v)	Polyvinylpyrrolidone (PVP)	-	50
vi)	Isopropyl alcohol	-	Lost in processing
vii)	Magnesium stearate	-	10
viii)	Talc	-	10

Sift ingredients (i), (ii), (iii) & (iv) and blend. Dissolve (v) in (vi) and granulate the blend. Dry and size the granules. Mix with ingredients (vii) and (viii), previously sifted & kept separately. Compress into tablets.

Example 3

	Ingredient		mg/tablet
i)	Amoxycillin sodium (equivalent to 500 mg Amoxycillin)	-	530

ii)	Lactose	-	50
iii)	Polyvinylpyrrolidone/Polyvinylacetate (PVP/PVA) co-polymer	-	125
iv)	Eudragit RL	-	25
v)	Magnesium stearate	-	5
vi)	Talc	-	5

Sift ingredients (i) to (vi). Separately blend (i), (ii), (iii) and (iv). Slug and de-slug the blend. Mix with ingredients (v) and (vi), previously sifted & kept separately. Compress into tablets.

Example 4

	Ingredient		**mg/tablet**
i)	Amoxycillin sodium (equivalent to 500 mg Amoxycillin)	-	530
ii)	Lactose	-	100
iii)	Eudragit RS	-	50
iv)	Eudragit RL	-	100
v)	Polyvinylpyrrolidone (PVP)	-	25
vi)	Isopropyl alcohol	-	Lost in processing
vii)	Magnesium stearate	-	5
viii)	Talc	-	5

Sift ingredients (i), (ii), (iii) & (iv) and blend. Dissolve (v) in (vi) and granulate the blend. Dry and size the granules. Mix with ingredients (vii) and (viii), previously sifted & kept separately. Compress into tablets.

Example 5

	Ingredient		**mg/tablet**
i)	Amoxycillin sodium (equivalent to 500 mg Amoxycillin)	-	530
ii)	Lactose	-	100
iii)	Eudragit RS	-	150
iv)	Polyvinylpyrrolidone (PVP)	-	25
v)	Isopropyl alcohol	-	Lost in processing
vi)	Magnesium stearate	-	5

vii)	Talc	-	5

Sift ingredients (i), (ii) & (iii) and blend. Dissolve (iv) in (v) and granulate the blend. Dry and size the granules. Mix with ingredients (vi) and (vii), previously sifted & kept separately. Compress into tablets.

Example 6

A	**Ingredient**		**mg/tablet**
i)	Amoxycillin sodium (equivalent to 500 mg Amoxycillin)	-	530
ii)	Lactose	-	100
iii)	Polyvinylpyrrolidone/Polyvinylacetate (PVP/PVA) co-polymer	-	175
iv)	Polyvinylpyrrolidone (PVP)	-	25
v)	Isopropyl alcohol	-	Lost in processing
vi)	Magnesium stearate	-	5
vii)	Talc	-	5
B	Clavulanate Potassium/ Microcrystalline Cellulose 1:1 mixture (equivalent to 125 mg Clavulanic acid)	-	250

1. Sift ingredients A (i), A(ii) & A(iii) and blend. Dissolve A(iv) in A(v) and granulate the blend. Dry and size the granules. Mix with ingredients A (vi) and A(vii), previously sifted.

2. Sift the blend B.

3. Compress the granules of step 1 and step 2 into inlay tablets.

Dated this 5th day of January 2004

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